Arabian Journal of Chemistry (2019) 12, 1496–1500

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Synthesis of novel rhodanine based functionalized furans from the reaction of *tert*-butyl isocyanide with acetylenic esters in the presence of rhodanine acetic acid derivatives

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Received 13 February 2013; accepted 8 October 2014
Available online 23 October 2014

KEYWORDS

Dialkyl acetylenedicarboxylate;
Multi-component reaction;
Rhodanine-N-acetic acid;
tert-Butyl isocyanide

Abstract The reactive 1:1 intermediate produced from the reaction of *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates was trapped by rhodanine-N-acetic acid derivatives to generate polyfunctionalized furan rings in fairly good yields.

1. Introduction

The chemistry of rhodanine and its derivatives, such as benzylidene rhodanine has been studied for over half a century because of their important chemical and biological applications. Rhodanine derivatives exhibit antibacterial, antiviral, anticonvulsant, anti-diabetic and anti-HIV-1 activities (Bursavich et al., 2007; Powers et al., 2006; Rawal et al., 2007; Zimenkovsky et al., 2006), and have been reported as uridined-iphospho-N-acetylmuramate/L-alanine ligase inhibitors (Sim et al., 2002). Despite the fact that the rhodanine based compounds exhibit a wide variety of bioactivities, the prevalence of rhodanine containing compounds of pharmaceutical interest is very small (Boyd, 1997).

On the other hand, functionalized furans represent an important synthetic building block and are present in a variety of biologically relevant natural products, such as calicogorgins, furan fatty acids, cytotoxic furan ocembranes, gersolanes, pseudopteranes, rosefuran, agassizin, furodysin, mikanifuran or α-clausenan (Bach and Kruger, 1999; Konig, 2001). Furans can also serve as important intermediates for many organic transformations (Feng et al., 2008). A recent report identified 2-aryl-5-(4-oxo-3-phen-ethyl-2-thioxothiazolidinylidenemethyl)-furans with rhodanine as a core molecule exhibiting anti-HIV-1 activity (Kamila et al., 2011). Therefore the combination of these two pharmacophores in the same molecule can be an interesting challenge for the development of new pharmacologically active molecules.

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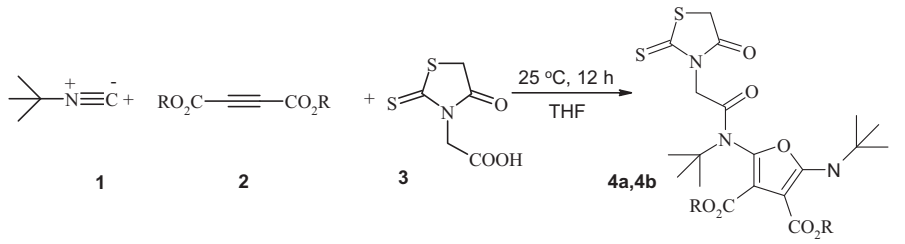
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2014.10.030
1878-5352



4	R	Yield (%)
a	Me	75
b	Et	70

6	R	R '	Yield (%)
a	C_6H_5	Me	85
b	C_6H_5	Et	80
c	C_6H_5-(p-CH_3)	Me	75
d	C_6H_5-(p-Cl)	Me	85
e	C_6H_5-(o-OMe)	Me	85

Scheme 1 Synthesis of diaminofuran derivatives.

In continuation of our studies on the development of new routes in the synthesis of novel heterocyclic compounds (Baharfar et al., 2011, 2008) such as uracil based furan derivatives (Baharfar and Baghbanian, 2012) and due to biological activities of rhodanine based compounds, we wish to report a simple multi-component reaction between *tert*-butyl isocyanide **1** and dialkyl acetylenedicarboxylates **2**, in the presence of 1-(carboxy methyl) rhodanine **3** and benzylidene rhodanine derivatives **5** leading to highly functionalized diaminofuran derivatives **4** and **6** (Scheme 1).

Therefore, *tert*-butyl isocyanide undergoes a smooth 2:1:1 addition reaction with dialkyl acetylenedicarboxylates **2** in the presence of 1-(carboxy methyl) rhodanine derivatives **3** in tetrahydrofuran at ambient temperature, to produce highly functionalized 2,5-diaminofuran derivatives **4** and **6** in 70–85% yield. The results are shown in Scheme 1.

2. Material and methods

Chemicals were purchased from Fluka and Merck companies. Melting points were determined in open capillaries using an Electrothermal 9100 apparatus. IR spectra were recorded using a Perkin-Elmer FT-IR 550 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer for the sample as indicated with the tetramethylsilane as an internal reference. MS spectra were recorded on a Finnigan MAT 44S, with an ionization voltage of 70 eV.

2.1. General synthesis of furan derivatives *4a–b*

To a magnetically stirred solution of rhodanine-3-acetic acid (1 mmol) and dialkyl acetylenedicarboxylates (1 mmol) in THF (5 ml), was added dropwise a solution of *tert*-butyl isocyanide (2 mmol) in THF (3 ml) over 10 min. The mixture was stirred for 12 h at room temperature in THF. After completion of the reaction, as indicated by TLC, the solvent was removed and the residue was purified by Silica gel flash chromatography to afford products **4a**,**b**.

2.2. General synthesis of furan derivatives *6a–e*

To a magnetically stirred solution of benzylidene rhodanine-3-acetic acid (1 mmol) and dialkyl acetylenedicarboxylates (1 mmol) in THF (5 ml), was added dropwise a solution of *tert*-butyl isocyanide (2 mmol) in THF (3 ml) over 10 min. The mixture was stirred for 12 h at reflux temperature in THF. After completion of the reaction, as indicated by TLC, the solvent was removed and the residue was purified by gradual removal of the solvent to afford products **6a–e**.

3. Results and discussion

The structures of isolated products **4a**,**b** and **6a–e** were deduced on the basis of IR, ^{1}H and ^{13}C NMR spectra, mass spectroscopy and elemental analysis. The mass spectrum of

4a displayed the molecular ion (M^+) peak at *m*/*z* 499, which is consistent with the 2:1:1 adduct of *tert*-butyl isocyanide, dimethyl acetylenedicarboxylate and 1-(carboxymethyl) rhodanine derivative. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibited four sharp singlets, readily recognized, arising from two *tert*-butyl (δ = 1.36 and 1.47) and two methoxy groups (δ = 3.78 and 3.92) protons a long with two AB systems (δ = 4.05 and 4.09, $^2J_{AB}$ = 18.0 Hz), (δ = 4.29 and 5.04, $^2J_{AB}$ = 16.0 Hz) for four protons of two methylene groups. Also, one broad singlet was observed at δ = 6.98 for the NH group. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 21 distinct resonances in agreement with the structure of **4a**.

A mechanistic rationalization for this reaction is provided in Scheme 2. On the basis of the well-established chemistry of isocyanides (Raut, 1995; Domling, 2006; Gulevich et al., 2010; Shaabani et al., 2011), it is reasonable to assume that the functionalized rhodanine based 2,5-diaminofurans **4** and **6** could result from an initial addition of the isocyanide **1** to the acetylenic ester **2** and subsequent protonation of the 1:1 adduct **7** by carboxylic acid **3**. Then, the positively charged ion **9** can be attacked by the carboxylate anion **8** to form imidoyl carboxylate **10**, which undergoes a Mumm rearrangement (Domling and Ugi, 2000; Ugi, 1997) under the reaction conditions, to produce the α,β-unsaturated intermediate **11**, followed by its trapping with isocyanide, to give the corresponding rhodanine based 2,5-diaminofurans **4** and **6**.

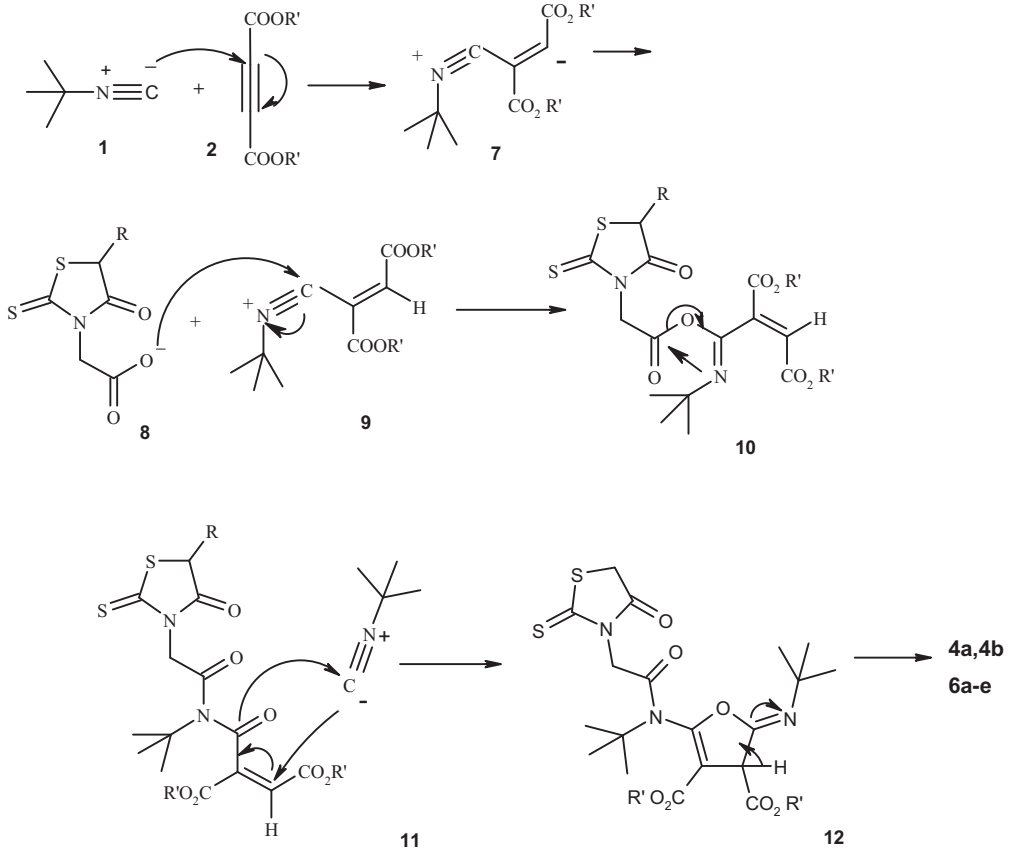
3.1. Physical and spectral data for the synthesized compounds

*3.1.1. Dimethyl 2-(tert-butylamino)-5-{tert-butyl[(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetyl]amino}furan-3,4-dicarboxylate (**4a**)*

Yellow powder, m.p. 138–143 °C, yield: 75%, IR (KBr) (ν_{max}, cm^{-1}): 3346 (NH), 1605, 1680 and 1740 (4 C═O), 1254 (C═S), ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.36 and 1.47 (2s, 18H, 2t-Bu), 3.78 and 3.92 (2s, 6H, $2OCH_3$), 4.05 and 4.09 (2d, 2H, AB system, $^2J_{HH}$ = 18.0 Hz, CH_2), 4.29 and 5.04 (2d, 2H, AB system, $^2J_{HH}$ = 16.0 Hz, CH_2), 6.98 (1s, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.9 and 29.7 ($2CMe_3$), 35.6 (CH_2), 46.9 (CH_2), 51.2 and 61.6 ($2CMe_3$), 52.6 and 52.9 ($2OCH_3$), 85.8 (C_4 of furan), 115.6 (C_3 of furan), 136.7 (C_5 of furan), 160.0 (C_2 of furan), 162.7, 165.0, 165.7 and 173.1 (4 C═O), 200.9 (C═S).

*3.1.2. Diethyl 2-(tert-butylamino)-5-{tert-butyl[(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetyl]amino}furan-3,4-dicarboxylate (**4b**)*

Yellow powder, m.p. 176–179 °C, yield: 70%, IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 1601, 1664, 1701 and 1744(4 C═O), 1257 (C═S), ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.31 and 1.40 (2t, 6H, $^3J_{HH}$ = 7.2 Hz, $2CH_3$), 1.38 and 1.47 (2s, 18H, 2t-Bu), 4.04 and 4.10 (2d, 2H, AB system, $^2J_{HH}$ = 18.0 Hz,



Scheme 2 Mechanistic pathways for the synthesis of the functionalized rhodanine based 2,5-diaminofurane derivatives.

CH_2), 4.21–4.42 (m, 4H, $2OCH_2$), 4.31 and 5.05 (2d, 2H, AB system, $^2J_{HH}$ = 16.0 Hz, CH_2), 6.95 (s, 1H, NH), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1 and 14.3 ($2CH_3$), 27.9 and 29.8 ($2CMe_3$), 35.6 (CH_2), 47.1 (CH_2), 52.9 and 59.9 ($2CMe_3$), 61.5 and 61.8 ($2OCH_2$), 86.1 (C_4 of furan), 116.0 (C_3 of furan), 136.0 (C_5 of furan), 159.8 (C_2 of furan), 162.5, 164.6, 165.9 and 173.1 (4 C=O), 200.9 (C=S).

*3.1.3. Dimethyl 2-[{[(5E)-5-benzylidine-4-oxo-2-thioxo-1,3-thiazolidine-3-yl]acetyl}(tert-butyl)amino]-5-(tert-butylamino)furan-3,4-dicarboxylate (**6a**)*

Yellow powder, m.p. 178–180 °C, yield: 85%, IR (KBr) (ν_{max}, cm^{-1}): 3360 (NH), 1603, 1680, 1713 and 1742(4 C=O), 1280 (C=S), ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.29 and 1.44 (2s, 18H, 2t-Bu), 3.69 and 3.84 (2s, 6H, $2OCH_3$), 4.28 and 5.02 (2d, 2H, AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 6.90 (s, 1H, NH), 7.54–7.68 (m, 5H, 5CH, Ar), 7.89 (s, 1H, CH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 27.8 and 29.6 ($2CMe_3$), 47.1 (CH_2), 51.6 and 61.3 ($2CMe_3$), 53.1 and 53.2 ($2OCH_3$), 85.8 (C_4 of furan), 115.8 (C_3 of furan), 122.5 (Cq, Ar), 130.0, 131.2 and 131.7 (5CH, Ar), 133.3 (Cq), 134.3 (CH), 136.2 (C_5 of furan), 159.5 (C_2 of furan), 163.0, 164.0, 166.0 and 166.7 (4 C=O), 193.8 (C=S).

*3.1.4. Diethyl 2-[{[(5E)-5-benzylidine-4-oxo-2-thioxo-1,3-thiazolidine-3-yl]acetyl}(tert-butyl)amino]-5-(tert-butylamino)furan-3,4-dicarboxylate (**6b**)*

Yellow powder, m.p. 156–162 °C, yield: 80%, IR (KBr) (ν_{max}, cm^{-1}): 3333 (NH), 1604, 1667, 1709 and 1736 (4 C=O), 1252 (C=S), ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.22 and 1.32 (2t, 6H, $^3J_{HH}$ = 7.2 Hz, $2CH_3$), 1.29 and 1.43 (2s, 18H, 2t-Bu), 4.12–4.33 (m, 4H, $2OCH_2$), 4.30 and 5.00 (2d, 2H, AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 6.89 (s, 1H, NH), 7.53–7.59 (m, 3H, 3CH, Ar), 7.66 (d, 2H, $^3J_{HH}$ = 6.8 Hz, 2CH, Ar), 7.88 (s, 1H, CH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.4 and 14.6 ($2CH_3$), 27.8 and 29.7 ($2CMe_3$), 47.2 (CH_2), 53.1and 60.0 ($2CMe_3$), 61.3 and 62.0 ($2OCH_2$), 85.9 (C_4 of furan), 116.2 (C_3 of furan), 122.5 (Cq, Ar), 130.0, 131.2 and 131.6 (5CH, Ar), 133.3 (Cq), 134.3 (CH), 135.8 (C_5 of furan), 159.5 (C_2 of furan), 162.5, 163.7, 166.0 and 166.7 (4 C=O), 193.8 (C=S).

*3.1.5. Dimethyl 2-(tert-Butylamino)-5-(tert-butyl{[(5E)-5-(4-methylbenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]acetyl}amino)furan-3,4-dicarboxylate (**6c**)*

Yellow powder, m.p. 180–182 °C, yield: 75%, IR (KBr) (ν_{max}, cm^{-1}): 3364 (NH), 1597 and 1724 (4 C=O), 1279 (C=S), ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.29 and 1.44 (2s, 18H, 2t-Bu), 2.38 (s, 3H, CH_3), 3.69 and 3.84 (2s, 6H, $2OCH_3$), 4.28 and 5.01 (2d, 2H, AB system, $^2J_{HH}$ = 16.0 Hz, CH_2), 6.90 (1s, 1H, NH), 7.39 (d, 2H, $^3J_{HH}$ = 8.0 Hz, 2CH, Ar), 7.56 (d, 2H, $^3J_{HH}$ = 8.4 Hz, 2CH, Ar), 7.84 (s, 1H, CH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 21.6 (CH_3, Ar), 27.8 and 29.6 ($2CMe_3$), 47.1 (CH_2), 51.6 and 61.3 ($2CMe_3$), 53.1 and 53.2 ($2OCH_3$), 85.8 (C_4 of furan), 115.8 (C_3 of furan), 121.2, 131.3 (2Cq, Ar), 130.6 and 130.7 (4CH, Ar), 134.4 (Cq), 136.3 (C_5 of furan), 142.2 (CH), 159.5 (C_2 of furan), 163.0, 164.1, 166.0 and 166.8 (4 C=O), 193.7 (C=S).

*3.1.6. Dimethyl 2-(tert-butylamino)-5-(tert-butyl{[(5E)-5-(4-chlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-acetyl}amino)furan-3,4-dicarboxylate (**6d**)*

Yellow powder, m.p. 180–183 °C, yield: 85%, IR (KBr) (ν_{max}, cm^{-1}): 3366 (NH), 1598, 1646 and 1704 (4 C=O) 1279 (C=S), ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.29 and 1.44 (2s, 18H, 2t-Bu), 3.69 and 3.84 (2s, 6H, $2OCH_3$), 4.28 and 5.02 (2d, 2H, AB system, $^2J_{HH}$ = 16.0 Hz, CH_2), 6.90 (1s, 1H, NH), 7.63 and 7.69 (2d, 4H, AB system, $^3J_{HH}$ = 8.4 Hz, 4CH, Ar), 7.88 (s, 1H, CH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 27.8 and 29.6 ($2CMe_3$), 47.2 (CH_2), 51.6 and 61.3 ($2CMe_3$), 53.1 and 53.2 ($2OCH_3$), 85.8 (C_4 of furan), 115.9 (C_3 of furan), 123.2 and 132.2 (2Cq, Ar), 130.1, 132.8 (4CH, Ar), 133.5 (Cq), 136.2 (CH), 136.3 (C_5 of furan), 159.5 (C_2 of furan), 163.0, 164.0, 165.9 and 166.7 (4 C=O), 193.5 (C=S).

*3.1.7. Dimethyl 2-(tert-butylamino)-5-(tert-butyl{[(5E)-5-(2-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-acetyl}amino)furan-3,4-dicarboxylate (**6e**)*

Yellow powder, m.p. 190–196 °C, yield: 85%, IR (KBr) (ν_{max}, cm^{-1}): 3354 (NH), 1597, 1675 and 1708 (4 C=O), 1252 (C=S), ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.38 and 1.49 (2s, 18H, 2t-Bu), 3.80, 3.91 and 3.95 (3s, 9H, $3OCH_3$), 4.43 and 5.20 (2d, 2H, AB system, $^2J_{HH}$ = 16.0 Hz, CH_2), 6.94 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH, Ar), 7.00 (s, 1H, NH), 7.05 (t, 1H, $^3J_{HH}$ = 8.0 Hz, CH, Ar), 7.41 (d, 1H, $^3J_{HH}$ = 8.4 Hz, CH, Ar), 7.42 (t, 1H, $^3J_{HH}$ = 8.4 Hz, CH, Ar), 8.14 (s, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.9 and 29.8 ($2CMe_3$), 46.9 (CH_2), 51.2 and 61.6 ($2CMe_3$), 52.7, 52.9 and 55.5 ($3OCH_3$), 85.8 (C_4 of furan), 111.2, 121.0, 122.8, 129.7 (4CH, Ar), 115.5 (C_3 of furan), 122.5 and 160.0 (2Cq), 130.2 (Cq), 132.7 (CH), 136.9 (C_5 of furan), 158.6 (C_2 of furan), 162.7, 165.0, 165.9 and 167.3 (4 C=O), 194.2 (C=S).

4. Conclusions

In summary, we have described a novel, efficient and simple method for the synthesis of rhodanine based furan derivatives of potential synthetic and pharmaceutical interest. Further investigation into the present method will be required to establish its utility and scope.

Acknowledgment

We are thankful to the Research Council of Mazandaran University for the financial support of this work.

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